



THE UNIVERSITY *of* EDINBURGH

## Edinburgh Research Explorer

# Kinetics and Mechanism of the Arase-Hoshi R<sub>2</sub>BH-Catalyzed Alkyne Hydroboration: Alkenylboronate generation via B-H/C-B Metathesis

### Citation for published version:

Nieto-sepulveda, E, Bage, AD, Evans, LA, Hunt, TA, Leach, AG, Thomas, SP & Lloyd-jones, GC 2019, 'Kinetics and Mechanism of the Arase-Hoshi R<sub>2</sub>BH-Catalyzed Alkyne Hydroboration: Alkenylboronate generation via B-H/C-B Metathesis', *Journal of the American Chemical Society*, vol. 141, no. 46, pp. 18600–18611. <https://doi.org/10.1021/jacs.9b10114>

### Digital Object Identifier (DOI):

[10.1021/jacs.9b10114](https://doi.org/10.1021/jacs.9b10114)

### Link:

[Link to publication record in Edinburgh Research Explorer](#)

### Document Version:

Peer reviewed version

### Published In:

Journal of the American Chemical Society

### General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

### Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact [openaccess@ed.ac.uk](mailto:openaccess@ed.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.



# Kinetics and Mechanism of the Arase-Hoshi $R_2BH$ -Catalyzed Alkyne Hydroboration: Alkenylboronate generation via B-H/C-B Metathesis.

Eduardo Nieto-Sepulveda,<sup>†‡</sup> Andrew D. Bage,<sup>†‡</sup> Louise A. Evans,<sup>†</sup> Thomas A. Hunt,<sup>‡</sup> Andrew G. Leach,<sup>‡</sup> Stephen P. Thomas\*,<sup>†</sup> and Guy C. Lloyd-Jones\*,<sup>†</sup>

<sup>†</sup> EaStChem, University of Edinburgh, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ, UK

<sup>‡</sup> Medicinal Chemistry, Oncology R&D, AstraZeneca, Cambridge, CB4 0WG, UK.

<sup>‡</sup> School of Health Sciences, Stopford Building, The University of Manchester, Oxford Road, Manchester M13 9PT, UK

**ABSTRACT:** The mechanism of  $R_2BH$ -catalyzed hydroboration of alkynes by 1,3,2-dioxaborolanes has been investigated by in situ  $^{19}F$  NMR spectroscopy, kinetic simulation, isotope entrainment, single-turnover labelling ( $^{10}B/^2H$ ), and density functional theory (DFT) calculations. For the  $Cy_2BH$  catalyzed hydroboration 4-fluorophenylacetylene by pinacolborane, the resting state is the anti-Markovnikov addition product  $ArCH=CHBCy_2$ . Irreversible and turnover-rate limiting reaction with pinacolborane ( $k \sim 7 \times 10^{-3} M^{-1}s^{-1}$ ) regenerates  $Cy_2BH$  and releases  $E$ - $Ar-CH=CHBpin$ . Two irreversible events proceed in concert with turnover. The first is a Markovnikov hydroboration leading to regioisomeric  $E$ - $Ar-CH(Bpin)=CH_2$ . This is unreactive to pinacolborane at ambient temperature, resulting in catalyst inhibition every  $\sim 10^2$  turnovers. The second is hydroboration of the alkenylboronate to give  $ArCH_2CH(BCy_2)Bpin$ , again leading to catalyst inhibition. 9-BBN behaves analogously to  $Cy_2BH$ , but with higher anti-Markovnikov selectivity, a lower barrier to secondary hydroboration, and overall lower efficiency. The key process for turnover is B-H/C-B metathesis, proceeding by stereospecific transfer of the  $E$ -alkenyl group within a transient,  $\mu$ -B-H-B bridged, 2-electron-3-centre bonded B-C-B intermediate.

## INTRODUCTION

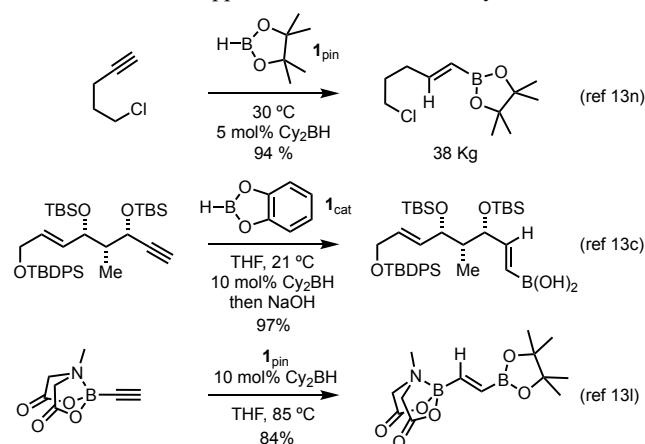
Alkenylboron reagents are ubiquitous in synthesis and pre-eminent in stereospecific cross-coupling reactions to generate alkenes. In such reactions, selection of the appropriate reagent can be crucial.<sup>1</sup> For example, although vinylboronic acid is not especially prone to protodeboronation,<sup>2</sup> in solution,<sup>2b</sup> it does polymerize<sup>3</sup> and self-condense,<sup>4</sup> making protected forms more readily handled.<sup>5</sup> Alkenylboronates are valued for their stability,<sup>6</sup> and as intermediates in the synthesis of alkenyl-boronic acid,<sup>7a</sup> -trifluoroborate,<sup>7b</sup> -tin,<sup>7c</sup> and -aluminium reagents,<sup>7d</sup> alkenyl iodonium salts,<sup>7e</sup> allyl boronates,<sup>7f</sup> epoxyboronates,<sup>7g</sup> and cyclopropylboronates.<sup>7h</sup>

Alkyne hydroboration allows regio- and stereo-selective synthesis of alkenylboron reagents.<sup>8</sup> Although many B-H species hydroborate alkynes at ambient temperature,<sup>8</sup> 1,3,2-dioxaborinanes,<sup>9a</sup> and 1,3,2-dioxaborolanes, such as catecholborane (**1**<sub>cat</sub>)<sup>9b</sup> and pinacolborane (**1**<sub>pin</sub>),<sup>9c</sup> are inert.<sup>9</sup> This has prompted the development of numerous catalysts,<sup>10,11</sup> and initiators,<sup>12</sup> for the process,<sup>8</sup> including Ca, Ti, Zr, Fe, Ru, Ni, Co, Rh, Ir, Cu, Au and Ag complexes/salts,<sup>10a-t</sup> carboxylic acids,<sup>10u</sup> amides,<sup>10v</sup> NaOH,<sup>10w</sup>  $Et_3P$ ,<sup>10x</sup> Al hydrides and alkyls,<sup>10yz</sup> and a wide range of boron species.<sup>11a-o</sup>

In 1995, Arase and Hoshi reported that  $Cy_2BH$  and 9-BBN both efficiently catalyze the regioselective *cis*-hydroboration of alkynes with **1**<sub>cat</sub> in THF at ambient temperature.<sup>11d</sup> The process was later extended to hydroboration with **1**<sub>pin</sub>, allowing preparation of  $E$ -alkenyl pinacolboronates in good yield,<sup>11f</sup> without contamination by metal catalysts. Over the last two decades, the Arase-Hoshi  $R_2BH$ -catalyzed alkyne hydroboration<sup>11d-g</sup> has been deployed extensively,<sup>13</sup> for example in the synthesis of Dictyostatin,<sup>13a</sup> Mandelalide A,<sup>13b</sup> (-)-FR182877,<sup>13cd</sup> Amphidinolide V,<sup>13e</sup> (+)-Herboxidiene,<sup>13f</sup> (-)-Bafilomycin A1,<sup>13gh</sup> Aigialomycin D,<sup>13i</sup> 1 $\alpha$ ,25-dihydroxyvitamin D analogues,<sup>13j</sup> Lejimalide B and analogues,<sup>13k</sup>

Burke's  $E$ -1-Bpin-2-MIDA ethene,<sup>13l</sup> enantioenriched geminal silylboronates,<sup>13m</sup> and at multikilo-scale in the preparation of an alkenylboronate for cyclopropanation.<sup>13n</sup> However, despite diverse and extensive application of the Arase-Hoshi hydroboration, remarkably little mechanistic detail has emerged regarding why it is highly effective in many cases,<sup>13</sup> e.g. Scheme 1, yet fails in others.<sup>14</sup>

**Scheme 1.** Selected applications of Arase-Hoshi hydroboration.<sup>13cln</sup>

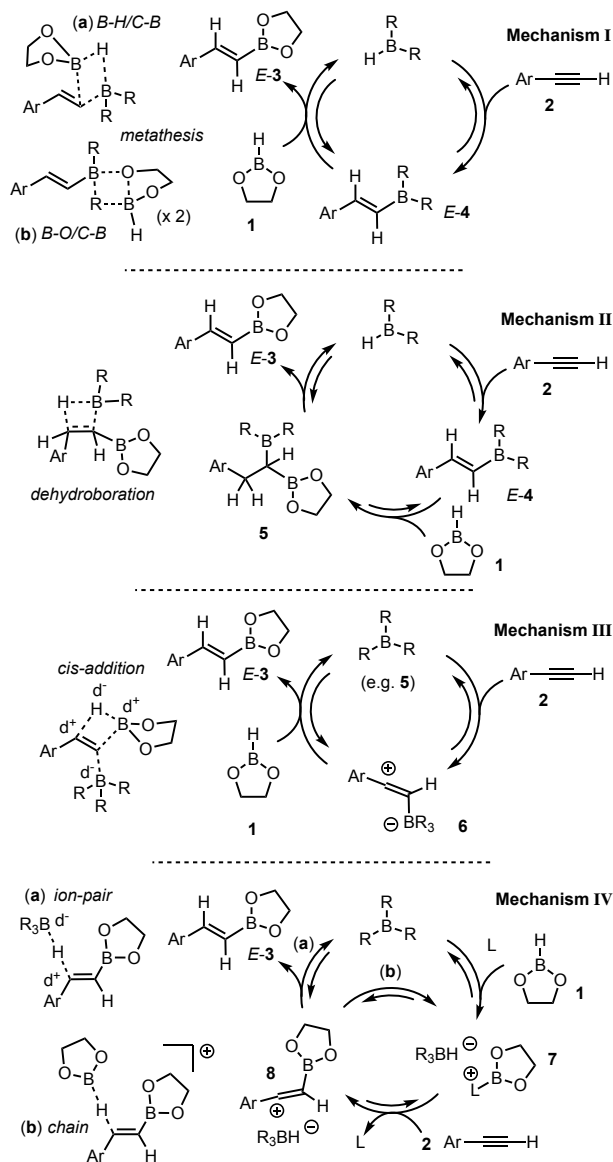


## RESULTS AND DISCUSSION

**1. Prior Studies.** In their seminal report,<sup>11df</sup> Arase and Hoshi suggested general mechanism I, Scheme 2, to account for the catalytic effect of  $R_2BH$  on alkyne hydroboration. The mechanism is analogous to that proposed in 1990 by Periasamy for catalysis by  $[H_3B \cdot N(Ph)Et_2]^{11ac}$  and was primarily based on two known stoichiometric processes: the hydroboration of alkynes by dialkylboranes,<sup>15</sup> and the thermal redistribution of trialkyl boranes with borate esters,<sup>10v,16</sup> including *o*-phenylene borate,<sup>16b</sup> and **1**<sub>cat</sub>.<sup>10v</sup>

Thermal redistribution of boranes with borates is catalyzed by *B*-H boranes.<sup>16d</sup> It may proceed by *B*-H/C-B metathesis (pathway Ia), as suggested by Köster,<sup>16d</sup> or by alkoxy ligand exchange (*B*-O/C-B metathesis; pathway Ib), as suggested by Brown,<sup>16b</sup> or by analogous processes where R = H.<sup>17</sup>

**Scheme 2.** Mechanisms I-IV for  $R_2BH/BR_3$ -catalyzed alkyne (2) hydroboration with a generic 1,3,2-dioxaborolane (1). Key product-generating steps are indicated on the left-hand side of each cycle. R = H, alkyl or Ar; L = neutral ligand, e.g. solvent.



Whilst the mechanism under Arase-Hoshi catalysis conditions has not been explored, a number of studies on related alkyne hydroborations using  $1_{pin}$ , that are catalyzed or initiated<sup>12</sup> by  $[Ar_{(3-n)}BH_n]$  species have been reported.<sup>11i-j,l,n</sup> Detailed NMR spectroscopic studies by Oestreich<sup>11i</sup> revealed that  $Ar_3B$  catalyzed hydroboration, where Ar = 3,5-( $CF_3$ )<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, involves *in situ*  $Ar_3B/1_{pin}$  redistribution to generate a range of species, including dimers of  $Ar_2BH$ , and  $ArBH_2$ . These were proposed to be the active catalysts for alkyne hydroboration via mechanism I. In contrast, Stephan and Glorius, found that alkyne hydroboration catalyzed by  $B(C_6F_5)_3$ , and by  $HB(C_6F_5)_2$ , involved generation of alkyldiaryl borane intermediates, including diboryl  $5_{pinAr}$  (Scheme 2, Mechanism II, R =  $C_6F_5$ ) that was isolated and characterized as an isonitrile complex.<sup>11j</sup> Alkyl boranes undergo thermal dehydroboration,<sup>17</sup> and a three-stage

hydroboration, hydroboration, dehydroboration sequence ( $2 \rightarrow 4 \rightarrow 5 \rightarrow 3$ ; mechanism II) provides a pathway for catalysis.<sup>18</sup> Independently prepared  $5_{pinAr}$  is an efficient catalyst for the alkyne hydroboration process; however, tests for dehydroboration from  $5_{pinAr}$  proved negative.<sup>11j</sup> This led to the suggestion that  $Ar_3B$ , or  $5_{pinAr}$ , or analogous  $RBAr_2$  species, exert catalysis through the Lewis-acid polarization<sup>19</sup> of the alkyne to facilitate the direct addition of the pinacolborane  $1_{pin}$  B-H, *cis* across a formally zwitterionic intermediate (6, mechanism III).<sup>11j</sup> Vasko, Kamer, and Aldrich recently reported on alkyne hydroboration catalyzed by a dimethylxanthene-based frustrated Lewis pair (FLP).<sup>11o</sup> It was elucidated that the active catalyst is generated in two stages: the FLP undergoes metathesis with  $1_{pin}$  to generate a  $(C_6F_5)_2(H)B \cdot PAR_3$  complex, and this then reacts with the alkyne (2) to generate *E*-4 (R = R =  $C_6F_5$ ). By analogy to prior work,<sup>11j</sup> *E*-4 was assumed to undergo hydroboration to generate  $5_{pinAr}$  and thus initiate mechanism III.<sup>11o</sup> An additional process to be considered is one in which a borenium-borohydride ion-pair (7, mechanism IV) is generated by hydride transfer from 1,3,2-dioxaborolane 1 to  $R_3B$ . Borenium-catalyzed hydroborations involving NHC species are well-described.<sup>20</sup> Propagation of Arase-Hoshi catalysis by mechanism IV would require H-transfer to alkyne adduct 8, within the ion-pair (pathway IVa), or by a chain-reaction involving 1 (pathway IVb). Mechanisms III and IV are partially analogous to that proposed by Ingleson for the addition of Lewis-base adducts of 9-BBN to alkynes,<sup>21</sup> however, the latter proceeds with overall *trans* addition of B and H.<sup>22</sup>

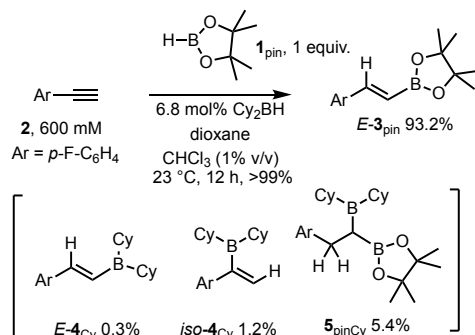
Herein we report on a mechanistic investigation of Arase-Hoshi hydroboration catalysis,<sup>11d-g</sup> Scheme 1, employing  $Cy_2BH$ , and 9-BBN, with  $1_{pin}$ . We have focussed in particular on the mode of addition of  $1_{pin}$  to *p*-fluorophenylacetylene (2) with the aim of distinguishing stepwise 1,2-addition involving metathesis (mechanism I), from direct *cis*-1,2-addition then dehydroboration (mechanism II), from direct *cis*-1,2-addition (mechanism III), from stepwise 1,2-addition, that does not involve C-B bond formation with the catalyst (mechanism IV).

**2. Elimination of 'Uncatalyzed' Reactions.** There are conflicting reports in the literature regarding the direct hydroboration of alkynes by 1,3,2-dioxaborolanes (1).<sup>9</sup> Thus, although it is widely accepted that  $1_{cat}^{9b}$  is relatively unreactive to simple alkynes, frequently requiring heating under solvent-free conditions,<sup>23</sup> pinacolborane,  $1_{pin}$ ,<sup>9c</sup> is sometimes reported to react efficiently with alkynes at ambient temperature in solution.<sup>9c,24,25</sup> 1,3,2-Dioxaborolanes (1) can undergo disproportionation,<sup>26</sup> especially in the presence of nucleophilic Lewis bases,<sup>26a</sup> to generate borates and  $BH_3$ . The latter is a known catalyst for alkyne hydroboration,<sup>11mn</sup> and thus impure or aged solutions, of  $1_{pin}$ , or those prepared *in situ* from pinacol and  $H_3B \cdot SMe_2$ ,<sup>9c</sup> can contain sufficient  $BH_3$  to undergo efficient but *indirect* (i.e. catalyzed)<sup>11n</sup> reaction with alkynes. We began by confirming<sup>25</sup> that, in the absence of a deliberately introduced catalyst,<sup>10,11</sup>  $1_{pin}$  does not react with alkyne 2 in solution at 23 °C, or undergo disproportionation to generate  $B_2pin_3 + BH_3$ , and hydroboration products thereof. Of a range of solvents explored, a mixture of dioxane and  $CHCl_3$  (1%) emerged as highly effective at stabilizing  $1_{pin}$ ,<sup>27</sup> and there was no detectable reaction of  $1_{pin}$  with 2 (600 mM) over a period of 24 hours at ambient temperature (99.9 % 2, <sup>19</sup>F NMR spectroscopy; >99%  $1_{pin}$ , <0.2 %  $B_2pin_3$ , <sup>11</sup>B NMR spectroscopy).

**3. In situ <sup>19</sup>F NMR Spectroscopic Analysis.** Addition of  $Cy_2BH$  to the stable solution of  $1_{pin}$  and 2 induces catalytic hydroboration, Scheme 3. Endpoint <sup>19</sup>F NMR spectroscopic analysis indicates that the product mixture contains *E*-3<sub>pin</sub> (93%) and three minor components, linear alkenylborane *E*-4<sub>Cy</sub> (0.3 %), branched alkenylborane *iso*-4<sub>Cy</sub> (1.2 %), and 1,1-diborylalkane  $5_{pinCy}$  (5.4%). Variation of the catalyst loading led to changes in the relative proportions of the endpoint reaction products. Diboryl  $5_{pinCy}$ , the product of formal double hydroboration,<sup>28</sup> was always generated in quantities directly

proportional to the  $\text{Cy}_2\text{BH}$  catalyst loading. In contrast, higher  $\text{Cy}_2\text{BH}$  loadings led to reduced quantities of  $E\text{-}3_{\text{pin}}$ .

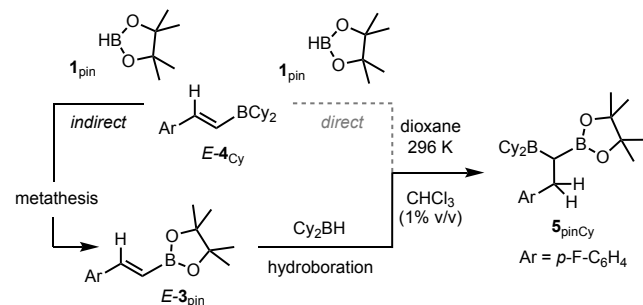
**Scheme 3.** HBCy<sub>2</sub>-catalyzed hydroboration of alkyne **2**, together with intermediates and side-products detected by <sup>19</sup>F-NMR spectroscopy after 12 h at 23 °C.



In situ <sup>19</sup>F NMR spectroscopic monitoring of the reaction evolution, Scheme 3, indicates that the branched alkenylborane  $iso\text{-}4_{\text{Cy}}$  is generated in concert with product  $E\text{-}3_{\text{pin}}$ , in a constant ratio of  $1:89 \pm 1$ . In contrast, alkenylborane  $E\text{-}4_{\text{Cy}}$  is generated transiently, reaching a maximum pseudo steady-state concentration after a short induction period. Increased catalyst loadings result in directly proportional increases in the concentration of transient alkenylborane  $E\text{-}4_{\text{Cy}}$ .<sup>29</sup> In contrast, diboryl  $5_{\text{pinCy}}$  is present in low concentrations until >99% of alkyne **2** has been consumed. At this stage, the concentration of product ( $E\text{-}3_{\text{pin}}$ ) becomes constant, the concentration of alkenylborane  $E\text{-}4_{\text{Cy}}$  decays to zero, and diboryl  $5_{\text{pinCy}}$  appears in direct inverse proportion to the decay in  $E\text{-}4_{\text{Cy}}$ . Identical kinetics were obtained in the absence of  $\text{CHCl}_3$  (1%).<sup>30</sup> Changing from dioxane to THF as solvent had negligible impact on the temporal concentrations of the species detected by <sup>19</sup>F NMR spectroscopy (**2**,  $E\text{-}3_{\text{pin}}$ ,  $E\text{-}4_{\text{Cy}}$ ,  $iso\text{-}4_{\text{Cy}}$ , and  $5_{\text{pinCy}}$ ). Standard graphical analysis of the concentration of **2** during its  $\text{Cy}_2\text{BH}$ -catalyzed reaction (Scheme 3) with **1**<sub>pin</sub>, and systematic variation in the concentrations of all three components led to an empirical rate equation  $d[\mathbf{3}_{\text{pin}}]/dt \approx k_{\text{obs}}[\text{Cy}_2\text{BH}]_0[\mathbf{1}_{\text{pin}}]_t$ , consistent with all four mechanisms (I-IV), under specific constraints.

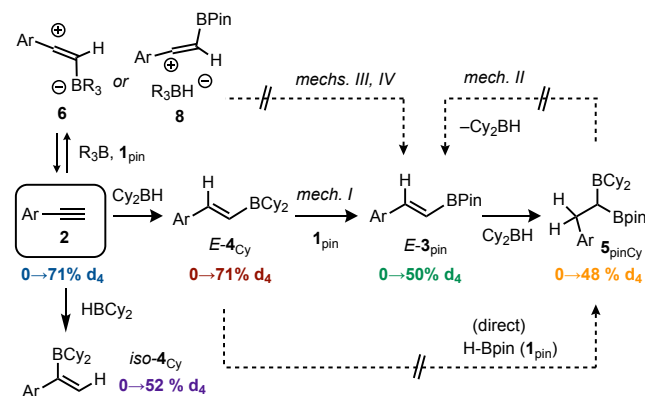
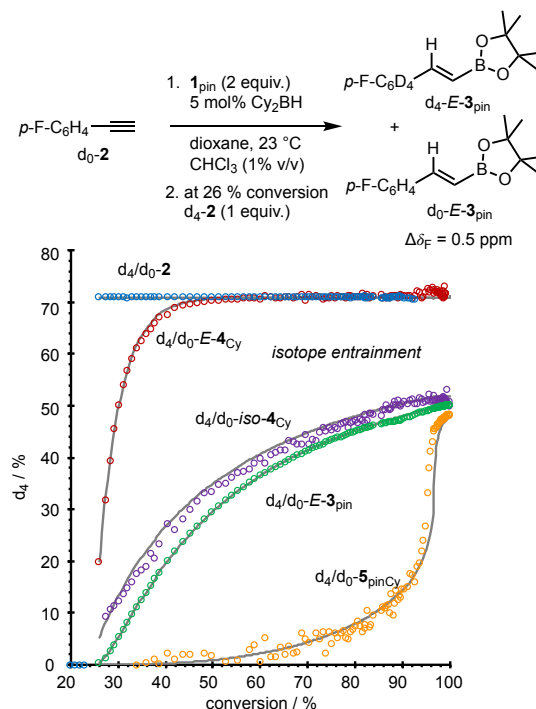
The generation of  $E\text{-}4_{\text{Cy}}$ ,  $iso\text{-}4_{\text{Cy}}$  and 1,1-diborylalkane  $5_{\text{pinCy}}$  were further investigated by stoichiometric reactions. In the absence of **1**<sub>pin</sub>, 1 equiv. of  $(\text{Cy}_2\text{BH})_n$  reacted instantly with **2** to give  $E\text{-}4_{\text{Cy}}$  and  $iso\text{-}4_{\text{Cy}}$  in an 89/1 ratio. Addition of 1 equiv. **1**<sub>pin</sub> to the mixture cleanly generated 1,1-diborylalkane  $5_{\text{pinCy}}$  from  $E\text{-}4_{\text{Cy}}$ , Scheme 4. The same product ( $5_{\text{pinCy}}$ ) was also cleanly generated on reaction of isolated purified  $E\text{-}3_{\text{pin}}$  with 1 equiv. HBCy<sub>2</sub>. Deconvolution of the direct versus indirect pathways from  $E\text{-}4_{\text{Cy}}$  to  $5_{\text{pinCy}}$  (Scheme 4) was achieved by isotopic labelling, *vide infra*.

**Scheme 4.** Stoichiometric hydroboration of alkenylboron species.<sup>15,28</sup> See text for full discussion of direct versus indirect reaction pathways from  $E\text{-}4_{\text{Cy}}$  to  $5_{\text{pinCy}}$ .



**4. Validation of Alkenylborane  $E\text{-}4$  as an On-Cycle Intermediate.** Having identified that  $E\text{-}4_{\text{Cy}}$  is generated at a pseudo steady-state concentration that corresponds to the  $\text{Cy}_2\text{BH}$  catalyst

loading, and that 1,1-diborylalkane  $5_{\text{pinCy}}$  primarily accumulates after **2** has been consumed, we sought to test whether  $E\text{-}4_{\text{Cy}}$  and  $5_{\text{pinCy}}$  are intrinsic to the catalytic cycle (e.g. in mechanisms I and II), or are peripheral to the cycle, e.g. generated by non-productive side reactions. Preparation of  $d_4\text{-}2$ , in which the aromatic ring is perdeuterated, results in an upfield shift ( $\Delta\delta = 0.5$  ppm) in the <sup>19</sup>F NMR spectra of  $d_4\text{-}2$ , relative to **2**, and analogously into any products thereof. This facilitates detailed interrogation of mechanisms I-IV, by way of isotope-entrainment.<sup>31</sup>



**Figure 1.** Isotope entrainment into the catalytic cycle, confirming on-cycle productivity of intermediate  $E\text{-}4_{\text{Cy}}$  ( $\rightarrow E\text{-}3_{\text{pin}}$ ) and its *indirect* conversion to  $5_{\text{pinCy}}$  via  $E\text{-}3_{\text{pin}}$ . Open circles: experimental data (<sup>19</sup>F NMR spectroscopy) for  $d_4$ -incorporation (%) versus net conversion of  $d_4/d_0\text{-}2$  +  $d_4/d_0\text{-}4_{\text{Cy}}$  into  $d_4/d_0\text{-}E\text{-}3_{\text{pin}}$ ,  $d_4/d_0\text{-}iso\text{-}4_{\text{Cy}}$ , and  $d_4/d_0\text{-}5_{\text{pinCy}}$  (%). Solid lines: simulation of  $d_4$ -incorporation based on the kinetic model in Figure 3. Conditions: **1**<sub>pin</sub> (600 mM), **2** (295 mM),  $\text{Cy}_2\text{BH}$ , (30 mM), dioxane/ $\text{CHCl}_3$  (99:1) at 296 K, with  $d_4\text{-}2$  (297 mM), added at 26% conversion.

Addition of  $d_4\text{-}2$  (0.5 equiv.) to a reaction of **2** (0.5 equiv.) and **1**<sub>pin</sub> (1 equiv.) undergoing turnover ( $\text{Cy}_2\text{BH}$ , 5 mol%) induces an isotopic perturbation. At the point of addition (26 % total conversion) the  $d_4/d_0$ -isotope ratio in the substrate pool **2**, is immediately raised from 0% to 71%- $d_4$ . In situ <sup>19</sup>F NMR spectroscopic monitoring of the subsequent evolution of the  $d_4/d_0$ -isotope ratios (%) in **2**,  $E\text{-}4_{\text{Cy}}$ ,

*iso*-4<sub>Cy</sub>, *E*-3<sub>pin</sub>, and 5<sub>pinCy</sub>, as a function of conversion, Figure 1, reveals numerous features:

i) There are no significant reversible reactions connecting **2** with any intermediates or products, on or off cycle: **2** remains 71%-d<sub>4</sub> throughout.

ii) The isotope ratio in transient intermediate *E*-4<sub>Cy</sub> grows, in advance of all other species except for **2** (which undergoes a step-change at the point of addition) and soon approaches the same level as **2**, i.e. 71%-d<sub>4</sub>.

iii) The isomeric alkenylborane *iso*-4<sub>Cy</sub>, generated in low proportion (1.2 % of total product), also accumulates d<sub>4</sub>, at a slower rate than *E*-4<sub>Cy</sub>, but in advance of *E*-3<sub>pin</sub>. It eventually reaches 52%-d<sub>4</sub>; this value corresponds exactly to that predicted for irreversible generation of *iso*-4<sub>Cy</sub> from **2**, as an inert product.

iv) Product *E*-3<sub>pin</sub> accumulates d<sub>4</sub> after addition of d<sub>4</sub>-**2**, rising to 50%-d<sub>4</sub> after a short induction period. The accumulation of d<sub>4</sub> in *E*-3<sub>pin</sub> is thus dependent on the growth of d<sub>4</sub> in an intermediate that connects it (mechanisms I, II) with the substrate **2**. Thus, *E*-3<sub>pin</sub> is not generated directly from **2**, or transiently complexed **2**, mechanisms III, IV).

v) On complete consumption of **2**, the intermediate, *E*-4<sub>Cy</sub> undergoes decay, but retains its isotope ratio throughout (71%-d<sub>4</sub>); it is thus generated and consumed irreversibly.

vi) 1,1-Diborylalkane 5<sub>pinCy</sub> is present in low quantities (0.5%) throughout the first 95 % of the reaction evolution, during which the isotope ratio in 5<sub>pinCy</sub> rises from 0 to 30%-d<sub>4</sub>. In the final stage of reaction evolution there is a surge in the concentration of 5<sub>pinCy</sub>, where it is generated in inverse proportion to the decay in *E*-4<sub>Cy</sub> (~5 mol%). However, the isotope ratio maximum in 5<sub>pinCy</sub> is 48%-d<sub>4</sub>, demonstrating that 5<sub>pinCy</sub> is not generated via turnover of *E*-4<sub>Cy</sub> (71%-d<sub>4</sub>) (mechanism II), but from *E*-3<sub>pin</sub> (<50%-d<sub>4</sub>) - i.e. the 'indirect' route, Scheme 4.

After complete consumption of **2**, addition of further **2** to the system (comprising *E*-3<sub>pin</sub>, *iso*-4<sub>Cy</sub>, 5<sub>pinCy</sub>, and 1<sub>pin</sub>) does not result in generation of *E*-4<sub>Cy</sub>, or recovery of any significant turnover, or perturbation in the isotope ratios of *E*-3<sub>pin</sub>, *iso*-4<sub>Cy</sub>, 5<sub>pinCy</sub>, confirming that all of observed species are generated irreversibly under the conditions of catalysis. Together with the empirical rate equation, the isotope entrainment analysis (Figure 1) eliminates mechanisms II, III and IV; and places considerable constraints on I in terms of (lack of) reversibility at all stages. Inclusion of these constraints, as illustrated in the simplified mechanism I at the bottom of Figure 1, allows quantitative prediction of the isotope ratios as function of conversion when the resting state is *E*-4<sub>Cy</sub>; see solid lines passing through data points in Figure 1, generated using the holistic kinetic model described below.

### 5. Single-Turnover <sup>10</sup>B,<sup>2</sup>H-analysis of Metathesis Pathways.

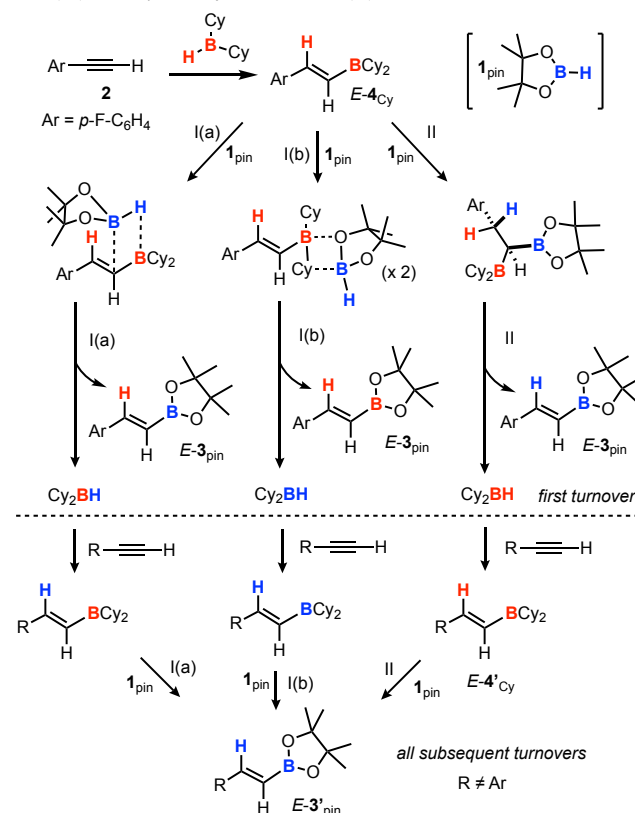
Attention was next focussed on the productive turnover of *E*-4<sub>Cy</sub> by 1<sub>pin</sub> to give Cy<sub>2</sub>BH + *E*-3<sub>pin</sub>. In common to metathesis mechanisms Ia and Ib, Scheme 2, is the retention of the *cis*-H in *E*-4<sub>Cy</sub> in the product *E*-3<sub>pin</sub>; see upper left-hand side of Scheme 5 where the *cis*-H in both *E*-4<sub>Cy</sub> and *E*-3<sub>pin</sub> is colored red. This provides simple differentiation of mechanism I from mechanism II. In the latter, the *cis*-H in *E*-4<sub>Cy</sub> is eliminated via *syn*-stereospecific dehydroboration during generation of *E*-3<sub>pin</sub>; see upper right-hand side of Scheme 5, where the liberated Cy<sub>2</sub>BH has B-H colored red. The two pathways for metathesis (Ia, Ib) are differentiated from each other by the boron atom in *E*-4<sub>Cy</sub> (colored red in the upper part of Scheme 5) which is transferred into Cy<sub>2</sub>BH in mechanism Ia, but retained in *E*-3<sub>pin</sub> in mechanism Ib.

In principle then, it is simple to distinguish mechanisms Ia, Ib, and II by <sup>1</sup>H/<sup>2</sup>H and <sup>10</sup>B/<sup>11</sup>B labelling of the Cy<sub>2</sub>BH catalyst and reagent 1<sub>pin</sub>, and analysis of the isotopic provenance of *cis*-H and B in the product *E*-3<sub>pin</sub>, as illustrated by red/blue coloring in Scheme 5.

However, two factors corrupt this analysis: i) for mechanism I, repeated catalytic turnover of Cy<sub>2</sub>BH generates *E*-3<sub>pin</sub> with a different label distribution to the first turnover, see lower section to Scheme 5; and ii) reversible generation of  $\mu$ -H borane dimers, scrambles the B-H/D labelling patterns in 1<sub>pin</sub> / Cy<sub>2</sub>BH. Neither problem is solved by stoichiometric reaction between *E*-4<sub>Cy</sub> and 1<sub>pin</sub>, because 1,1-diborylalkane 5<sub>pinCy</sub> is rapidly generated from Cy<sub>2</sub>BH + *E*-4<sub>Cy</sub> (Scheme 4) when there is no alkyne (**2**) present.

To bypass these complications, we conducted single turnover analysis<sup>32</sup> via sequential-additions of Cy<sub>2</sub>BH (cat.), then RC≡CH (R ≠ Ar), then 1<sub>pin</sub>, to the alkyne **2**. As illustrated schematically in the lower section of Scheme 5, this effects *in situ* generation of *E*-4<sub>Cy</sub> and its conversion to *E*-3<sub>pin</sub>, with the regenerated Cy<sub>2</sub>BH catalyst being sequestered in further turnover that converts RC≡CH to *E*-3'<sub>pin</sub> via *E*-4'<sub>Cy</sub>. The *E*-3<sub>pin</sub> emerging from the first turnover is then separated, and analyzed by <sup>1</sup>H and <sup>10</sup>/<sup>11</sup>B NMR spectroscopy, and by MS.

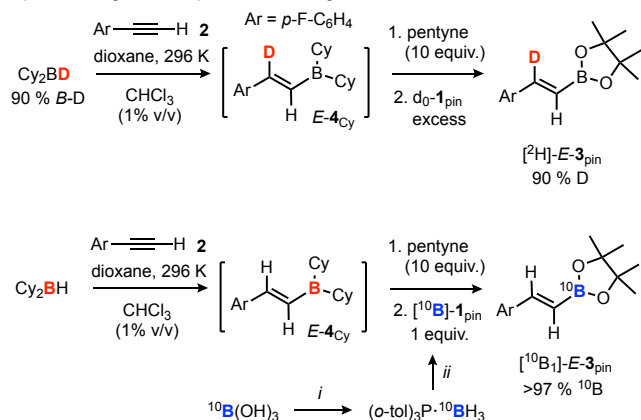
**Scheme 5.** H and B migrations (red, blue) under catalytic conditions during the first, and all subsequent turnovers, during conversion of on-cycle intermediate *E*-4<sub>Cy</sub> to *E*-3<sub>pin</sub> by 1<sub>pin</sub>. Coloring illustrates differentiation of B-H/C-B metathesis (Ia), B-O/C-B metathesis (Ib), and *syn*-dehydroboration (II) mechanisms.



Commercially-available D<sub>3</sub>B·THF was reacted with cyclohexene to generate (d<sub>n</sub>-Cy<sub>2</sub>)BD *in situ*. Control experiments (see SI) indicated 90% B-D. Single turnover analysis, using pentyne to sequester Cy<sub>2</sub>BH and 1<sub>pin</sub>, gave *E*-3<sub>pin</sub> that was 90 % deuterated at *cis*-H, Scheme 6. This is fully consistent with metathesis pathways Ia and Ib, and eliminates mechanism II. Labelling of the boron intermediates required development of a reliable synthesis of stable solutions of pure [<sup>10</sup>B]-1<sub>pin</sub>, ≥ 97% <sup>10</sup>B, in dioxane/CHCl<sub>3</sub>, Scheme 6 lower; see SI for full details. With [<sup>10</sup>B]-1<sub>pin</sub> in hand, single-turnover, followed by isolation of *E*-3<sub>pin</sub> and analysis by <sup>10</sup>B/<sup>11</sup>B NMR spectroscopy using natural abundance ArBF<sub>3</sub>K as an internal reference, indicated that [<sup>10</sup>B]-*E*-3<sub>pin</sub> (≥ 97% <sup>10</sup>B) is generated. This result is fully consistent with metathesis pathway Ia, and eliminates B-O/C-B metathesis (alkoxy ligand exchange, pathway Ib), Scheme 6.



**Scheme 6.** Single-turnover analysis<sup>a</sup> of *E*-**3**<sub>pin</sub> generated from Cy<sub>2</sub>BD + **1**<sub>pin</sub> and Cy<sub>2</sub>BH + <sup>10</sup>B-**1**<sub>pin</sub>.<sup>b</sup>



<sup>a</sup>Analyses by <sup>1</sup>H and <sup>10/11</sup>B NMR spectroscopy, and MS; see SI.

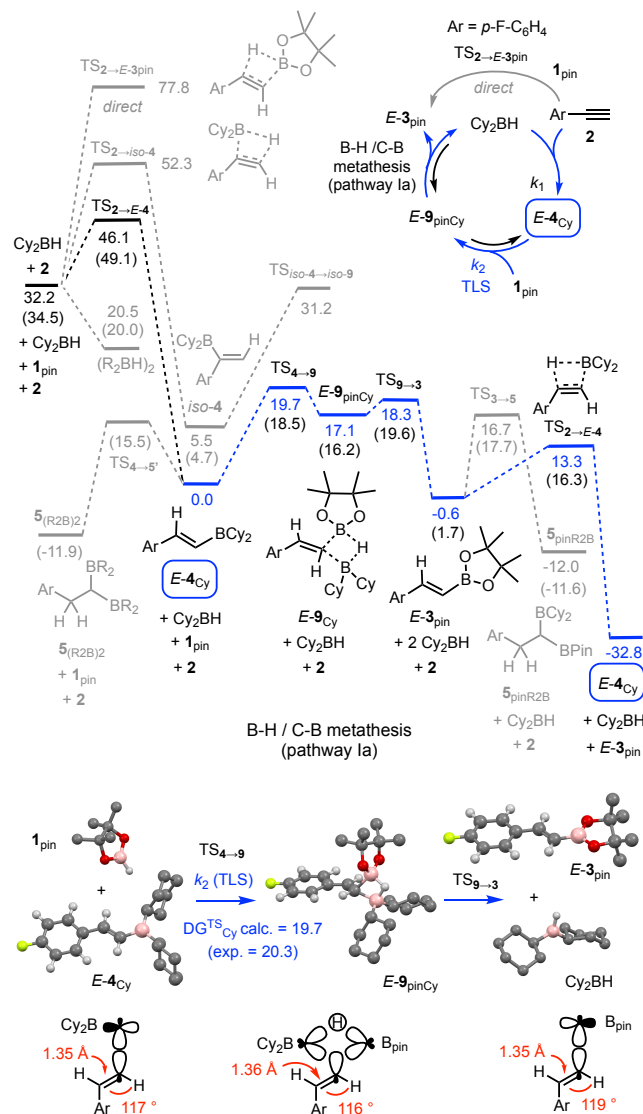
<sup>b</sup>Conditions: i) iPrOH, 3 equiv. CaH<sub>2</sub>, 4 equiv. 90 °C; distill 60 °C, 40-60 mBar; then LiAlH<sub>4</sub> 0.8 equiv, *o*-tol<sub>3</sub>P, 1.5 equiv. THF, 0 °C; then Rochelle salt, aq.; then 3% aq. H<sub>2</sub>O<sub>2</sub>; 52-72% ii) pinacol, 0.77 equiv., dioxane / CHCl<sub>3</sub> (1%), 57 °C, 16h, then distil, 40 °C, 60-90 mBar; 1.09 M solution in dioxane / CHCl<sub>3</sub>, 50% yield from pinacol.

**6. Mechanism and Kinetics of Cy<sub>2</sub>BH Catalysis via Alkenyl B-H/C-B Metathesis (pathway Ia).** The full catalytic cycle for Mechanism Ia was explored using the M06L/6-311++G\*\* level of theory, which had previously been found effective for the protodeboration reaction.<sup>33</sup> All calculations were performed in Gaussian09,<sup>34</sup> with dioxane solvation incorporated via a polarizable continuum model (PCM) single point at the same level of theory. Free energy corrections were computed with 'goodvibes'<sup>35</sup> at T = 298 and standard state concentration of 1M. Geometries and energies (including a description of the low energy conformations) are provided as supporting information.

The calculated barrier for the direct (uncatalyzed) reaction of **1**<sub>pin</sub> with **2** is very high ( $\Delta G^\ddagger_{\text{calc.}} = 46 \text{ kcal mol}^{-1}$ ), consistent with the requirement for catalysis.<sup>11j,m,o,25</sup> For catalysis by Cy<sub>2</sub>BH, the resting state was found to be *E*-**4**<sub>Cy</sub>. Metathesis by **1**<sub>pin</sub> (*k*<sub>2</sub>) is calculated to be turnover-rate limiting ( $\Delta G^\ddagger_{\text{calc.}} = 19.7 \text{ kcal mol}^{-1}$ ; Figure 2), in excellent agreement with the experimental rate of turnover,  $\Delta G^\ddagger_{\text{exp.}} = 20.3 \text{ kcal mol}^{-1}$ . Rapid capture of the liberated Cy<sub>2</sub>BH by **2** ( $\Delta G^\ddagger_{\text{calc.}} = 14 \text{ kcal mol}^{-1}$ ), completes the cycle, which is thus consistent with the empirical rate-equation in which the turnover frequency is first order in both **1**<sub>pin</sub> and [BCy<sub>2</sub>]<sub>tot</sub>. The B-H/C-B metathesis (pathway Ia) is calculated to proceed in a step-wise manner involving a transient  $\mu$ -H bridged intermediate (*E*-**9**<sub>pinCy</sub>) where a B-C-B assembly is midpoint between transfer of the alkene from one boron to the other, with retention of *E*-configuration (see lower section of Figure 2). Intermediate *E*-**9**<sub>pinCy</sub> is somewhat analogous to a number of isolated B-C-B and Al-C-Al complexes.<sup>36</sup> In a detailed study of a closely related structure, Holthausen and Wagner determined the bonding in this type of intermediate to involve two 2-electron-3-centre ('2e3c') bonds.<sup>36a</sup> The first employs the 1s orbital of the bridging hydrogen while the second employs an sp<sup>2</sup> hybrid orbital from the bridging carbon, see schematic illustration at the bottom Figure 2. In accordance with the nature of these previously described structures, the double bond is almost unperturbed in the intermediate *E*-**9**<sub>pinCy</sub> (C=C 1.36 Å, C=C-H 116°).

Whilst the thermodynamic driving force for overall hydroboration (**2** + **1**<sub>pin</sub> → *E*-**3**<sub>pin</sub>) is substantial<sup>37</sup> ( $\Delta G_{\text{calc.}} = -33 \text{ kcal mol}^{-1}$ ), that for the metathesis step *E*-**4**<sub>Cy</sub> + **1**<sub>pin</sub> → *E*-**3**<sub>pin</sub> + Cy<sub>2</sub>BH is low. The calculations, see Figure 2, also confirm that the disfavored Markovnikov hydroboration product *iso*-**4**<sub>Cy</sub> has a large barrier to metathesis

by **1**<sub>pin</sub> ( $\Delta G^\ddagger_{\text{calc.}} = 25.7 \text{ kcal mol}^{-1}$ ) and that **5**<sub>pinCy</sub> is generated irreversibly: dehydroboration to regenerate *E*-**3**<sub>pin</sub> + Cy<sub>2</sub>BH,  $\Delta G^\ddagger_{\text{calc.}} = 29 \text{ kcal mol}^{-1}$ . These features render generation of *iso*-**4**<sub>Cy</sub> and **5**<sub>pinCy</sub> catalyst termination steps, at ambient temperature.



**Figure 2.** Upper: free energies (kcal mol<sup>-1</sup>, M06L/6-311++G\*\* PCM (dioxane, single point with M06L/6-311++G\*\*) standard state, 1M, 298 K) of species in the reaction of **1**<sub>pin</sub> with **2** to generate *E*-**3**<sub>pin</sub>, via intermediates *E*-**4**<sub>Cy</sub> and *E*-**9**<sub>pinCy</sub>. Kinetically disfavored and inhibition pathways in grey; values in parentheses are for the analogous process with 9-BBN. Lower: calculated structures (H atoms on cyclohexyl and pinacolyl groups omitted for clarity) for the B-H/C-B metathesis process, with schematic illustration of the key orbitals and 2-electron-3-centre bonds.<sup>36a</sup>

With a more detailed mechanistic picture in hand, the full reaction evolution, as determined by in situ <sup>19</sup>F NMR spectroscopy, was explored across a range of initial concentrations. The kinetic model outlined in Figure 3, satisfactorily accounts for the temporal concentrations of all species detected by <sup>19</sup>F-NMR spectroscopy, Scheme 3, including generation of side product *iso*-**4**<sub>Cy</sub> and the secondary process that indirectly converts *E*-**4**<sub>Cy</sub> to **5**<sub>pinCy</sub>, via **3**<sub>pin</sub>, predominantly after complete consumption of **2**. The optimization of the model includes isotope entrainment of d<sub>4</sub>-**2** into the catalytic cycle, see solid lines through datapoints in Figure 1. Five key features emerge from the analysis:

i) The rate of hydroboration of alkyne **2** by  $\text{Cy}_2\text{BH}$  ( $k_1$ ) is far greater than the rate of reaction of  $E\text{-}4_{\text{Cy}}$  with  $\mathbf{1}_{\text{pin}}$  ( $k_2$ ), leading to  $E\text{-}4_{\text{Cy}}$  being the dominant catalyst species throughout the reaction.

ii) The selectivity for anti-Markovnikov hydroboration ( $k_1/k_3$ ) of **2** by  $\text{Cy}_2\text{BH}$  is moderate, leading to catalyst inhibition *via* generation of *iso*-**4**, occurring on average, once in every 89 turnovers.

iii) The rate of hydroboration of **2** by  $\text{Cy}_2\text{BH}$  ( $k_1$ ) is around three orders of magnitude faster than  $E\text{-}3_{\text{pin}}$  ( $k_4$ ), leading to the majority of  $\mathbf{5}_{\text{pinCy}}$  being generated in the very last stages of reaction, when all of the alkyne **2** has been consumed.

iv) The impact of  $\text{Cy}_2\text{BH}$  aggregation,<sup>38</sup> which is extensive in the absence of alkyne **2**, is negligible, due to the low concentration of free borane.

v) Generation of *iso*-**4**<sub>Cy</sub> and  $\mathbf{5}_{\text{pinCy}}$  reduces the yield of  $E\text{-}3_{\text{pin}}$ . In principle, the highest yield of  $E\text{-}3_{\text{pin}}$  attainable under these conditions is 98.5%, by use of 1.25 mol%  $\text{Cy}_2\text{BH}$ . This value assumes no catalyst deactivation pathways other than generation of *iso*-**4**<sub>Cy</sub> and  $\mathbf{5}_{\text{pinCy}}$ .

vi) Unlike 9-BBN, *vide infra*, competing hydroboration of  $E\text{-}4_{\text{Cy}}$  by  $\text{Cy}_2\text{BH}$  is negligible:  $\mathbf{5}_{(\text{Cy})2}$  was not detected under the reaction conditions ( $\leq 0.1\%$ ;  $k_1/k_5 \geq 2.7 \times 10^3$ ).

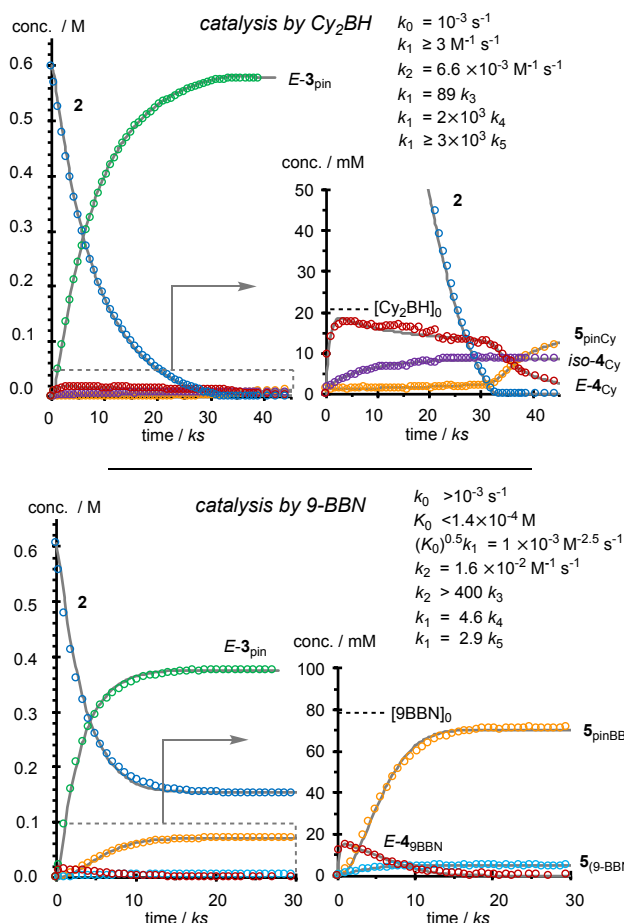
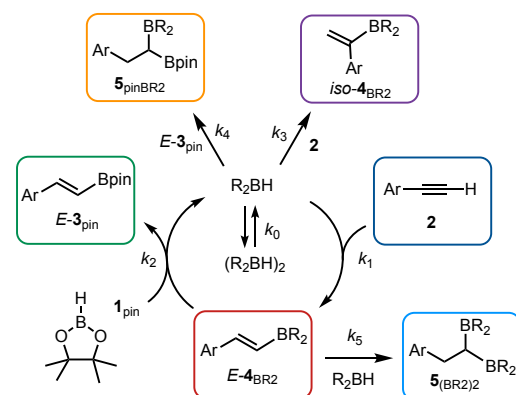
**7. Catalysis by 9-BBN.** Unlike the air-sensitive, in situ-prepared suspension of  $(\text{Cy}_2\text{BH})_n$ ,<sup>38</sup> the related secondary borane (9-BBN)<sub>2</sub>, is commercially-available as a crystalline solid, and as a readily-handled solution in THF. Although the majority of applications of (9-BBN)<sub>2</sub> catalysis in Arase-Hoshi alkyne hydroboration have employed  $\mathbf{1}_{\text{cat}}$ , it is also effective with  $\mathbf{1}_{\text{pin}}$  and has recently been used by Werner in the synthesis of *E*-stilbenes;<sup>39</sup> see SI for further examples. In situ <sup>19</sup>F-NMR spectroscopic analysis of the reaction of alkyne **2** with  $\mathbf{1}_{\text{pin}}$  catalyzed by (9-BBN)<sub>2</sub>, revealed a similar but not identical set of intermediates to those found for  $\text{Cy}_2\text{BH}$ . In situ <sup>11</sup>B NMR spectroscopic analysis also confirmed that the free 9-BBN is predominantly dimeric ( $K_0 < 1.4 \times 10^{-4}$  M;  $k_0 \sim 1 \times 10^{-3}$  s<sup>-1</sup>)<sup>40</sup> under the reaction conditions. Independent reaction of alkyne **2** with 9-BBN generated  $E\text{-}4_{9\text{BBN}}$  and the double hydroboration<sup>28</sup> product  $\mathbf{5}_{(9\text{BBN})2}$ , which was also detected (0.8%) during catalytic turnover. Reaction of isolated  $E\text{-}3_{\text{pin}}$  with 9-BBN generated  $\mathbf{5}_{\text{pin}9\text{BBN}}$ .

The catalytic cycle involving 9-BBN, generated by reversible dissociation from (9-BBN)<sub>2</sub>, was also explored using the M06L/6-311++G\*\* level of theory, and the computed energies (see values in parentheses in Figure 2 and further detail of inhibition processes) used to guide simulation of the full reaction evolution, as determined by in situ <sup>19</sup>F NMR spectroscopy, at two (9-BBN)<sub>2</sub> loadings. Hydroboration catalyzed by (9-BBN)<sub>2</sub> (Figure 3, lower graphs) has a distinct profile, with three key points identified by computational and kinetic analysis:

i) Dimerization of the free 9-BBN ( $k_0$ ) leads to a low pseudo steady-state concentration of  $E\text{-}4_{9\text{BBN}}$ . Higher catalyst concentrations result in decreased selectivity ( $k_2/k_5$ ) for  $E\text{-}3_{\text{pin}}$  over  $\mathbf{5}_{(9\text{BBN})2}$  (165/1 at 3 mol%; 75/1 at 6.8 mol% (9-BBN)<sub>2</sub>). Increasing the  $[\mathbf{1}_{\text{pin}}]_0/[\mathbf{2}]_0$  ratio leads to less  $\mathbf{5}_{(9\text{BBN})2}$  generation; however, with this substrate (**2**), this is only a minor inhibition pathway.

ii) The anti-Markovnikov selectivity ( $k_1/k_3$ ) in hydroboration of **2** by 9-BBN is high (>400/1) leading to negligible inhibition.

iii) The rate of hydroboration of the product  $E\text{-}3_{\text{pin}}$  by 9-BBN ( $k_4$ ; to generate  $\mathbf{5}_{\text{pin}9\text{BBN}}$ ) competes significantly with hydroboration of **2** ( $k_1/k_4 \sim 5$ ), leading to irreversible inhibition *throughout* the reaction, Figure 3. This reduces the maximum yield of  $E\text{-}3_{\text{pin}}$  under these conditions to 65 %, using 11 mol% (9-BBN)<sub>2</sub>.



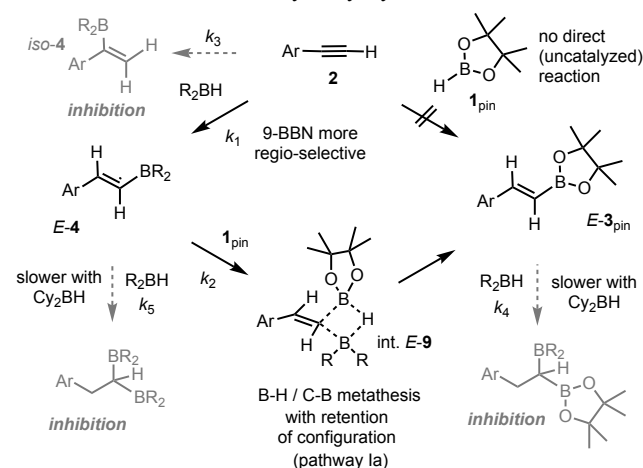
**Figure 3.** Temporal evolution of **2** (600 mM) +  $\mathbf{1}_{\text{pin}}$  (606 mM) at 296 K, in dioxane, containing 1 % v/v  $\text{CHCl}_3$  stabilizer, after addition of  $(\text{Cy}_2\text{BH})_n$ , 3.5 mol% (upper graphs) and (9-BBN)<sub>2</sub>, 6.8 mol% (lower graphs). Open circles experimental data (*in situ* <sup>19</sup>F NMR spectroscopy). Solid lines: simulations according to the kinetic models shown. For  $\text{Cy}_2\text{BH}$ ,  $k_0$  represents quasi-irreversible reactive dissolution of its suspension. For the 9-BBN simulation,  $K_0$  represents an upper limit based on <sup>11</sup>B NMR spectroscopic analysis; the absolute rate constants should not be applied in isolation. See SI for full details.

## 8. Catalyst Inhibition in Arase-Hoshi Hydroboration.

The secondary boranes  $\text{Cy}_2\text{BH}$  and 9-BBN catalyse Arase-Hoshi hydroboration of alkyne **2** with different efficiencies. As discussed above, the dominant 'on-cycle' catalytic species for the reaction is identified as  $\text{Ar-CH=CH-BR}_2$  (*E*-**4**), generated by irreversible anti-Markovnikov addition of the borane  $\text{R}_2\text{BH}$  to the alkyne (**2**). The relatively low barrier to irreversible reaction of *E*-**4** with  $\mathbf{1}_{\text{pin}}$  (~20

kcal mol<sup>-1</sup>) allows the overall process to undergo turnover at ambient temperature. For both catalyst systems, a number of competing and irreversible hydroborations by R<sub>2</sub>BH proceed in concert with turnover. These include Markovnikov hydroboration of the alkyne (to generate *iso*-4), addition to the on-cycle intermediate (*E*-4) to generate 5<sub>(R<sub>2</sub>B)<sub>2</sub>, and addition to the net hydroboration product (*E*-3<sub>pin</sub>) to generate 5<sub>pinR<sub>2</sub>B</sub>, all of which lead to catalyst inhibition and reduced yields. As a result, the two catalysts Cy<sub>2</sub>BH and 9-BBN have different optimum catalyst loadings; these reflect a compromise between total conversion of alkyne 2, and overall yield of *E*-3<sub>pin</sub>. Conducting the reaction at higher temperatures and in different solvents will change selectivity and may also facilitate turnover of what are inhibited species at ambient temperature in dioxane.</sub>

**Scheme 7.** Arase-Hoshi catalysis by Cy<sub>2</sub>BH versus 9-BBN.<sup>11df,13,37</sup>



For 1<sub>pin</sub> + *E*-4, the B-H/C-B-metathesis proceeds at a similar rate with 9-BBN ( $k_2 \sim 2 \times 10^{-2} \text{ M}^{-1}\text{s}^{-1}$ ) as compared to Cy<sub>2</sub>B ( $k_2 \sim 7 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ ), but with the addition of R<sub>2</sub>BH across the alkyne 2 proceeding with considerably higher regioselectivity (9-BBN,  $k_1/k_3 > 400$ ; Cy<sub>2</sub>B,  $k_1/k_3 \sim 89$ ), Scheme 7. Ostensibly, this suggests 9-BBN to be the superior catalyst. Indeed, many of the early applications of Arase-Hoshi hydroboration employed 9-BBN with 1<sub>cat</sub>.<sup>13</sup> However, 9-BBN has a higher propensity than Cy<sub>2</sub>BH to undergo secondary hydroboration<sup>28</sup> ( $k_4$ , *E*-3<sub>pin</sub> → 5<sub>pin9BBN</sub>; and  $k_5$ , *E*-4<sub>9BBN</sub> → 5<sub>(9BBN)<sub>2</sub>) leading to an earlier onset of termination of turnover. Hindered alkyne substrates that inhibit B-H/C-B-metathesis by 1, or those bearing B-coordinating groups that can direct secondary hydroboration,<sup>14</sup> will exacerbate catalyst termination. Lack of turnover of intermediates analogous to *E*-4, by 1<sub>pin</sub> or 1<sub>cat</sub> explains why some alkynes that fail to undergo Arase-Hoshi catalysis, readily undergo stoichiometric hydroboration with 9-BBN,<sup>14c</sup> or Cy<sub>2</sub>BH,<sup>14a</sup> and then direct cross-coupling.</sub>

## CONCLUSIONS

In 1990, Periasamy described modest acceleration of alkyne hydroboration by catecholborane 1<sub>cat</sub>, in the presence of [H<sub>3</sub>B·N(Ph)Et<sub>2</sub>]<sup>11ac</sup>. Five years later, Arase and Hoshi demonstrated that dialkyl boranes (R<sub>2</sub>BH) are very efficient catalysts for alkyne hydroboration by 1<sub>cat</sub><sup>11d</sup> and pinacolborane (1<sub>pin</sub>)<sup>11f</sup> to generate synthetically useful alkenylboronate reagents.<sup>6,8</sup> This mild, efficient, and highly-selective procedure has enjoyed diverse applications in synthesis,<sup>13,14</sup> Scheme 1. Herein we have described a mechanistic analysis of Cy<sub>2</sub>BH<sup>13</sup> and 9-BBN<sup>13,37</sup> catalyzed hydroboration of 4-fluorophenylacetylene (2) by 1<sub>pin</sub>. Isotopic entrapment (Figure 1) confirms the major catalyst-derived species, Ar-CH=CH-BR<sub>2</sub> (*E*-4), is productive and 'on-cycle', undergoing turnover-limiting reaction with pinacolborane<sup>9c</sup> ('H-Bpin', 1<sub>pin</sub>). M06L/6-311++G\*\* calculations (Figure 2), and single-turnover isotopic labelling (<sup>2</sup>H,<sup>10</sup>B; Scheme 6) indicate stereospecific two-stage B-H/C-B metathesis,

proceeding via a fleeting intermediate in which the alkene is pinched between two boron centres, by way of a μ-B-H-B bridge and a 2-electron-3-centre ('2e3c') B-C-B bond; Figure 2 and Scheme 7. This is the first direct experimental evidence for R<sub>2</sub>BH generation from an alkenylboron proceeding via B-C-B transfer (mechanism Ia),<sup>16d</sup> rather than by alkoxy ligand exchange (mechanism Ib).<sup>16a</sup> The process is directly analogous to the mechanism for redistribution reactions of alkylboranes proposed by Köster in the 1960s,<sup>16d</sup> and the B-Ar-B species isolated and characterized in great detail by Holthausen and Wagner.<sup>36a</sup> It is also related to the generation of arylboronate products in the FLP-catalyzed borylation of heteroarenes,<sup>41</sup> the 1<sub>pin</sub>-mediated liberation of Ar<sub>2</sub>BH and Ar<sub>2</sub>BH<sub>2</sub> from Ar<sub>3</sub>B species,<sup>11i</sup> and to Ar<sub>2</sub>BH liberation from a dimethylxanthene-based FLP.<sup>11o</sup> The kinetic and mechanistic details elucidated herein, will aid in the rational selection of conditions for application of Arase-Hoshi hydroboration,<sup>13,14</sup> as well as in the design of new selective boron-catalyzed reactions and processes.

## ASSOCIATED CONTENT

**Supporting Information:** Additional discussion, experimental procedures, kinetic data and analysis, computational details, characterization data and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Authors

[guy.lloyd-jones@ed.ac.uk](mailto:guy.lloyd-jones@ed.ac.uk), [stephen.thomas@ed.ac.uk](mailto:stephen.thomas@ed.ac.uk)

### Author contributions

† E.N.S. and A.D.B. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

### Funding Sources

G.C.L.-J. and E.N.S. thank CONACYT for generous support. S.P.T. thanks the Royal Society for a University Research Fellowship. S.P.T. and A.B.D. thank AstraZeneca and the EPSRC for a CASE award. The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° [340163].

## ACKNOWLEDGMENT

AGL thanks the EPSRC and National Chemical Database Service for access to the Cambridge Structural Database. We thank Matthew Harper (Bristol) for technical assistance in the early phases of this work, and Jeremy Harvey (Bristol, Leuven) for preliminary calculations and valuable mechanistic discussion.

## REFERENCES

- (1) Lennox, A. J.; Lloyd-Jones, G. C. Selection of boron reagents for Suzuki–Miyaura coupling. *Chem. Soc. Rev.*, **2014**, *43*, 412–443.
- (2) (a) Noonan, G.; Leach, A. G., A mechanistic proposal for the protodeboration of neat boronic acids: boronic acid mediated reaction in the solid state. *Org. Biomol. Chem.* **2015**, *13*, 2555–2560. (b) Cox, P. A.; Leach, A. G.; Campbell, A. D.; Lloyd-Jones, G. C. Protodeboration of Heteroaromatic, Vinyl, and Cyclopropyl Boronic Acids: pH–Rate Profiles, Autocatalysis, and Disproportionation. *J. Am. Chem. Soc.* **2016**, *138*, 9145–9157.
- (3) Matteson, D. S. Radical-catalyzed Additions to α,β-Unsaturated Boronic Esters. *J. Am. Chem. Soc.* **1960**, *82*, 4228–4233.



- (4) Kerins, F.; O'Shea, D. F. Generation of Substituted Styrenes via Suzuki Cross-Coupling of Aryl Halides with 2,4,6-Trivinylcycloboroxane. *J. Org. Chem.* **2002**, *67*, 4968-4971.
- (5) See for example: See e.g. Denmark, S. E.; Butler, C. R. Palladium- (and nickel-) catalyzed vinylation of aryl halides. *Chem. Commun.* **2009**, 20-33.
- (6) (a) Carreras, J.; Caballero, A.; Pérez, P. J. Alkenyl Boronates: Synthesis and Applications. *Chem. Asian J.* **2019**, *14*, 329-343
- (7) (a) Brown, H. C.; Gupta, S. K. Hydroboration. XXXIX. 1,3,2-Benzodioxaborole (catecholborane) as a new hydroboration reagent for alkenes and alkynes. General synthesis of alkane- and alkaneboronic acids and esters via hydroboration. Directive effects in the hydroboration of alkenes and alkynes with catecholborane. *J. Am. Chem. Soc.* **1975**, *97*, 5249-5255. (b) Molander, G. A.; Ellis, N. M. Highly Stereoselective Synthesis of cis-Alkenyl Pinacolboronates and Potassium cis-Alkenyltrifluoroborates via a Hydroboration/Protodeboronation Approach. *J. Org. Chem.* **2008**, *73*, 6841-6844. (c) Hoshi, M.; Hayatsu, T.; Okimoto, M.; Kodama, S. Transfer of Alk-1-enyl Group from Boron to Tin: A Highly Stereoselective Synthesis of (*E*)-Alk-1-enyltributylstannanes. *Synlett* **2009**, 2945-2948. (d) Hoshi, M.; Shirakawa, K. Transfer of alk-1-enyl group from boron to aluminium: a novel way to prepare (*E*)-alk-1-enyldiisobutylalanes. *Chem. Commun.* **2002**, 2146-2147. (e) Fujita, M.; Lee, H. J.; Okuyama, T. Stereochemical Inversion in the Vinylic Substitution of Boronic Esters To Give Iodonium Salts: Participation of the Internal Oxy Group. *Org. Lett.* **2006**, *8*, 1399-1401. (f) Shimizu, H.; Igarashi, T.; Miura, T.; Murakami, M. Rhodium-Catalyzed Reaction of 1-Alkenylboronates with Aldehydes Leading to Allylation Products. *Angew. Chem. Int. Ed.* **2011**, *50*, 11465-11469. (g) Li, J.; Burke, M. D. Pinene-Derived Iminodiacetic Acid (PIDA): A Powerful Ligand for Stereoselective Synthesis and Iterative Cross-Coupling of C(sp<sup>3</sup>) Boronate Building Blocks. *J. Am. Chem. Soc.* **2011**, *133*, 13774-13777. (h) Rubin, M.; Rubina, M.; Gevorgyan, V. Transition Metal Chemistry of Cyclopropenes and Cyclopropanes. *Chem. Rev.* **2007**, *107*, 3117-3179.
- (8) For a review see reference 6, and also: Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J.-J.; Arseniyadisb, S.; Smietana, M. Recent developments in alkyne borylations. *Tetrahedron*, **2014**, *70*, 8431-8452.
- (9) (a) Woods, W. G.; Strong, P. L. 4,4,6-Trimethyl-1,3,2-dioxaborinane. A Stable Dialkoxyborane. *J. Am. Chem. Soc.* **1966**, *88*, 4667-4671. (b) Brown, H. C.; Gupta, S. K. 1,3,2-Benzodioxaborole, a convenient monofunctional hydroborating agent. Simple new synthesis of alkaneboronic esters and acids from olefins via hydroboration. *J. Am. Chem. Soc.* **1971**, *93*, 1816-1818. (c) Tucker, C. E.; Davidson, J.; Knochel, P. Mild and Stereoselective Hydroborations of Functionalized Alkynes and Alkenes Using Pinacolborane. *J. Org. Chem.* **1992**, *57*, 3482-3485. (d) E. A. Luthile, J.; Pietruszka, J.; Witt, A. Enantiomerically pure 1,3,2-dioxaborolanes: new reagents for the hydroboration of alkynes. *Chem. Commun.* **1998**, 2651-2652.
- (10) See, for example: a) Harder, S.; Spielmann, J. Calcium-mediated hydroboration of alkenes: "Trojan horse" or "true" catalysis? *J. Organomet. Chem.* **2012**, *698*, 7-14. (b) Hartwig, J. F.; Muhoro, C. N. Mechanistic Studies of Titanocene-Catalyzed Alkene and Alkyne Hydroboration: Borane Complexes as Catalytic Intermediates. *Organometallics* **2000**, *19*, 30-38. (c) Pereira, S.; Srebnik, M. Hydroboration of Alkynes with Pinacolborane Catalyzed by HZrCp<sub>2</sub>Cl. *Organometallics* **1995**, *14*, 3127-3128. (d) Wang, Y. D.; Kimball, G.; Prashad, A. S.; Wang, Y. Zr-Mediated hydroboration: stereoselective synthesis of vinyl boronic esters. *Tetrahedron Lett.* **2005**, *46*, 8777-8780. (e) Greenhalgh, M. D.; Thomas, S. P. Chemo-, regio-, and stereoselective iron-catalysed hydroboration of alkenes and alkynes. *Chem. Commun.* **2013**, *49*, 11230-11232. (f) Haberberger, M.; Enthaler, S. Straightforward Iron-Catalyzed Synthesis of Vinylboronates by the Hydroboration of Alkynes. *Chem. Asian J.* **2013**, *8*, 50-54. (g) Szyling, J.; Franczyk, A.; Stefanowska, K.; Klarek, M.; Maciejewski, H.; Walkowiak, J. An Effective Catalytic Hydroboration of Alkynes in Supercritical CO<sub>2</sub> under Repetitive Batch Mode. *ChemCatChem* **2018**, *10*, 531-539 (h) Zaidlewicz, M.; Meller, J. Syntheses with organoboranes. X. Monohydroboration of conjugated enynes with catecholborane catalyzed by nickel(II) chloride complexes with diphosphines. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1049-1056. (i) Zaidlewicz, M.; Meller, J. Monohydroboration of Conjugated Dienes, Alkynes and Functionalized Alkynes with Catecholborane Catalyzed by Nickel(II) Chloride and Cobalt(II) Chloride Complexes with Phosphines. *Main Group Met. Chem.* **2000**, *23*, 765. (j) von Hahmann, C. N.; Talavera, M.; Xu, C.; Braun, T. Reactivity of 3,3,3-Trifluoropropene at Rhodium Complexes: Development of Hydroboration Reactions. *Chem. Eur. J.* **2018**, *24*, 11131-11138. (k) Dietz, M.; Johnson, A.; Martínez-Martínez, A.; Weller, A. S. The [Rh(Xantphos)]<sup>+</sup> catalyzed hydroboration of diphenylacetylene using trimethylamine-borane. *Inorganica Chim. Acta* **2019**, *491*, 9-13. (l) Merola, J. S.; Knorr, J. R. Synthesis and reaction chemistry of boryliridium hydride complexes formed by oxidative addition of catecholborane to iridium(I): Lessons for metal-catalyzed hydroboration. *J. Organomet. Chem.* **2014**, *750*, 86-97. (m) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Copper-Catalyzed Highly Regio- and Stereoselective Directed Hydroboration of Unsymmetrical Internal Alkynes: Controlling Regioselectivity by Choice of Catalytic Species. *Chem. Eur. J.* **2012**, *18*, 4179-4184. (n) Romero, E. A.; Jazsar, R.; Bertrand, G. (CAAC)CuX-catalyzed hydroboration of terminal alkynes with pinacolborane directed by the X-ligand. *J. Organomet. Chem.* **2017**, *829*, 11-13. (o) Jang, W. J.; Lee, W. L.; Moon, J. H.; Lee, J. Y.; Yun, J. Copper-Catalyzed trans-Hydroboration of Terminal Aryl Alkynes: Stereodivergent Synthesis of Alkenylboron Compounds. *Org. Lett.* **2016**, *18*, 1390-1393. (p) Lipshutz, B. H.; Bošković, Ž. V.; Aue, D. H. Synthesis of Activated Alkenylboronates from Acetylenic Esters by CuH-Catalyzed 1,2-Addition/Transmetalation. *Angew. Chem. Int. Ed.* **2008**, *47*, 10183-10186. (q) Pereira, S.; Srebnik, M. A study of hydroboration of alkenes and alkynes with pinacolborane catalyzed by transition metals. *Tetrahedron Lett.* **1996**, *37*, 3283-3286. (r) Leyva, A.; Zhang, X.; Corma, A. Chemoselective hydroboration of alkynes vs. alkenes over gold catalysts. *Chem. Commun.* **2009**, 4947-4949. (s) Mamidala, R.; Pandey, V. K.; Rit, A. AgSbF<sub>6</sub>-Catalyzed anti-Markovnikov hydroboration of terminal alkynes. *Chem. Commun.* **2019**, *55*, 989-992. (t) Wang, Y.; Guan, R.; Sivaguru, P.; Cong, X.; Bi, X. Silver-Catalyzed anti-Markovnikov Hydroboration of C-C Multiple Bonds. *Org. Lett.* **2019**, *21*, 4035-4038. (u) Ho, H. E.; Asao, N.; Yamamoto, Y.; Jin, T. Carboxylic Acid-Catalyzed Highly Efficient and Selective Hydroboration of Alkynes with Pinacolborane. *Org. Lett.* **2014**, *16*, 4670-4673. (v) Garrett, C. E.; Fu, G. C. Hydroboration of Olefins with Catecholborane at Room Temperature in the Presence of N,N-Dimethylacetamide. *J. Org. Chem.* **1996**, *61*, 3224-3225. (w) Wu, Y.; Shan, C.; Ying, J.; Su, J.; Zhu, J.; Liu, L. L.; Zhao, Y. Catalytic hydroboration of aldehydes, ketones, alkynes and alkenes initiated by NaOH. *Green Chem.* **2017**, *19*, 4169-4175. (x) Fritzemeier, R.; Gates, A.; Guo, X.; Lin, Z.; Santos, W. L. Transition Metal-Free Trans Hydroboration of Alkynoic Acid Derivatives: Experimental and Theoretical Studies. *J. Org. Chem.* **2018**, *83*, 10436-10444. (y) Yang, Z.; Zhong, M.; Ma, X.; Nijesh, K.; De, S.; Parameswaran, P.; Roesky, H. W. An Aluminum Dihydride Working as a Catalyst in Hydroboration and Dehydrocoupling. *J. Am. Chem. Soc.* **2016**, *138*, 2548-2551. (z) Bismuto, A.; Thomas, S. P.; Cowley, M. J. Aluminum Hydride Catalyzed Hydroboration of Alkynes. *Angew. Chem. Int. Ed.* **2016**, *55*, 15356-15359.
- (11) (a) Suseela, Y.; Prasad, A. S. B.; Periasamy, M. Catalytic Effect of a BH<sub>3</sub>:N,N-Diethylaniline Complex in the Formation of Alkenyl Catecholboranes from Alk-1-yne and Catecholborane. *J. Chem. Soc., Chem. Commun.* **1990**, 446-447. (b) Arase, A.; Nunokawa, Y.; Masuda, Y.; Hoshi, M. LiBH<sub>4</sub>-promoted hydroboration of alkenes with 1,3,2-benzodioxaborole. *J. Chem. Soc.,*

- Chem. Commun.* **1991**, 205-206. (c) Suseela, Y.; Periasamy, M. Convenient method for the preparation of catecholborane and promotion of the formation of alkenyl catecholborane using  $\text{BH}_3$  complexes. *J. Organomet. Chem.* **1993**, *450*, 47-52. (d) Arase, A.; Hoshi, M.; Mijin, A.; Nishi, K. Dialkylborane-Catalyzed Hydroboration of Alkynes with 1,3,2-Benzodioxaborole in Tetrahydrofuran. *Synthetic Communications* **1995**, *25*, 1957-1962. (e) Hoshi, M.; Shirakawa, K.; Arase, A. Transfer of alk-1-enyl group from boron to boron: preparation of B-[(*E*)-alk-1-enyl]-9-borabicyclo[3.3.1]nonane. *Chem. Commun.* **1998**, 1225-1226. (f) Shirakawa, K.; Arase, A.; Hoshi, M. Preparation of (*E*)-1-Alkenylboronic Acid Pinacol Esters via Transfer of Alkenyl Group from Boron to Boron. *Synthesis* **2004**, 1814-1820. (g) Hoshi, M.; Shirakawa, K.; Okimoto, M. Generation of bis(pentafluorophenyl)borane-dimethyl sulfide complex as a solution of hexane and its application to hydroboration of alk-1-yne with pinacolborane. *Tetrahedron Lett.* **2007**, *48*, 8475-8478. (h) Boussomniere, A.; Pan, X.; Geib, S. J.; Curran, D. P. Borenum-Catalyzed Hydroborations of Silyl-Substituted Alkenes and Alkynes with a Readily Available N-Heterocyclic Carbene-Borane. *Organometallics* **2013**, *32*, 7445-7450. (i) Yin, Q.; Kemper, S.; Klare, H. F. T.; Oestreich, M. Boron Lewis Acid-Catalyzed Hydroboration of Alkenes with Pinacolborane:  $\text{BAr}^{\text{F}}_3$  Does What  $\text{B}(\text{C}_6\text{F}_5)_3$  Cannot Do! *Chem. Eur. J.* **2016**, *22*, 13840-13844. (j) Fleige, M.; Mobus, J.; vom Stein, T.; Glorius, F.; Stephan, D. W. Lewis acid catalysis: catalytic hydroboration of alkynes initiated by Piers' borane. *Chem. Commun.* **2016**, 52, 10830-10833. (k) Yin, Q.; Soltani, Y.; Melen, R. L.; Oestreich, M.  $\text{BAr}^{\text{F}}_3$ -Catalyzed Imine Hydroboration with Pinacolborane Not Requiring the Assistance of an Additional Lewis Base. *Organometallics* **2017**, *36*, 2381-2384. (l) Lawson, J. R.; Wilkins, L. C.; Melen, R. L. Tris(2,4,6-trifluorophenyl)borane: An Efficient Hydroboration Catalyst. *Chem. Eur. J.* **2017**, *23*, 10997-11000. (m) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. A.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. Rhodium(I) catalysed dimerization of (*E*)-styrylboronate esters: molecular structures of (*E*)- $p\text{-MeO-C}_6\text{H}_4\text{-CH=CH-B(1,2-O}_2\text{C}_6\text{H}_4)_3$  and  $p\text{-MeO-C}_6\text{H}_4\text{-CH}_2\text{C}\{\text{B(1,2-O}_2\text{C}_6\text{H}_4)_3\}_3$ . *J. Organomet. Chem.* **2002**, *652*, 77-85. (n) Ang, N. W. J.; Buettner, C. S.; Docherty, S.; Bismuto, A.; Carney, J. R.; Docherty, J. H.; Cowley, M. J.; Thomas, S. P. Borane-Catalysed Hydroboration of Alkynes and Alkenes. *Synthesis* **2018**, *50*, 803-808. (o) Vasko, P.; Zulkifly, I. A.; Fuentes, M. Á.; Mo, Z.; Hicks, J.; Kamer, P. C. J.; Aldridge, S. Reversible C-H Activation, Facile C-B/B-H Metathesis and Apparent Hydroboration Catalysis by a Dimethylxanthene-Based Frustrated Lewis Pair. *Chem. Eur. J.* **2018**, *24*, 10531-10540. (p) Carden, J. L.; Gierlich, L. J.; Wass, D. F.; Browne, D. L.; Melen, R. L. Unlocking the catalytic potential of tris(3,4,5-trifluorophenyl)borane with microwave irradiation. *Chem. Commun.* **2019**, 55, 318-321.
- (12) Initiators can function by inducing disproportionation (see reference 26) of the 1,3,2-dioxaborolane (**1**), leading to generation of  $\text{BH}_3$ , a known catalyst for Arase-Hoshi alkyne hydroboration (see references 11m,n). It is thus not clear for the examples in references 10 and 11, which additives are genuine (pre)-catalysts, and which are initiators.
- (13) Selected examples of the application of Arase-Hoshi  $\text{R}_2\text{BH}$ -catalyzed alkyne hydroboration in synthesis: (a) Jägel, J.; Maier, M. E. An Efficient Synthesis of the C1-C9 Segment of Dictyostatin. *Synlett* **2006**, 693-696. (b) Lei, H.; Yan, J.; Yu, J.; Liu, Y.; Wang, Z.; Xu, Z.; Ye, T. Total Synthesis and Stereochemical Reassignment of Mandelalide A. *Angew. Chem. Int. Ed.* **2014**, *53*, 6533-6537. (c) Evans, D. A.; Starr, J. T. A cycloaddition cascade approach to the total synthesis of (-)-FR182877. *J. Am. Chem. Soc.* **2003**, *125*, 13531-13540. (d) Evans, D. A.; Starr, J. T. A Cascade Cycloaddition Strategy Leading to the Total Synthesis of (-)-FR182877. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787-1790. (e) Fürstner, A.; Flügge, S.; Larionov, O.; Takahashi, Y.; Kubota, T.; Kobayashi, J. i. Total Synthesis and Biological Evaluation of Amphidinolide V and Analogues. *Chem. Eur. J.* **2009**, *15*, 4011-4029.
- (f) Pellicena, M.; Krämer, K.; Romea, P.; Urpi, F. Total Synthesis of (+)-Herboxidiene from Two Chiral Lactate-Derived Ketones. *Org. Lett.* **2011**, *13*, 5350-5353. (g) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. Total Synthesis of (-)-Bafilomycin A<sub>1</sub>: Application of Diastereoselective Crotylboration and Methyl Ketone Aldol Reactions. *Angew. Chem. Int. Ed.* **1999**, *38*, 1652-1655. (h) Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. M.; Fegley, G. J.; Roush, W. R. Total Synthesis of (-)-Bafilomycin A<sub>1</sub>. *J. Am. Chem. Soc.* **2002**, *124*, 6981-6990. (i) Chrovian, C. C.; Knapp-Reed, B.; Montgomery, J. Total Synthesis of Aigialomycin D: Surprising Chemoselectivity Dependence on Alkyne Structure in Nickel-Catalyzed Cyclizations. *Org. Lett.* **2008**, *10*, 811-814. (j) Minne, G.; Verlinde, L.; Verstuyf, A.; De Clercq, P. J. Synthesis of 1 $\alpha$ ,25-Dihydroxyvitamin D Analogues Featuring a S<sub>2</sub>-symmetric CD-ring Core. *Molecules* **2009**, *14*, 894-903. (k) Gagnepain, J.; Moulin, E.; Nevado, C.; Waser, M.; Maier, A.; Kelter, G.; Fiebig, H.-H.; Fürstner, A. Molecular Editing and Assessment of the Cytotoxic Properties of Iejimalide and Progeny. *Chem. Eur. J.* **2011**, *17*, 6973-6984. (l) Struble, J. R.; Lee, S. J.; Burke, M. D. Ethynyl MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis. *Tetrahedron* **2010**, *66*, 4710-4718. (m) Szymaniak, A. A.; Zhang, C.; Coombs, J. R.; Morken, J. P. Enantioselective Synthesis of Nonracemic Geminal Silylboronates by Pt-Catalyzed Hydrosilylation. *ACS Catal.* **2018**, *8*, 2897-2901. (n) Bassan, E. M.; Baxter, C. A.; Beutner, G. L.; Emerson, K. M.; Fleitz, F. J.; Johnson, S.; Keen, S.; Kim, M. M.; Kuethe, J. T.; Leonard, W. R.; Mullens, P. R.; Muzzio, D. J.; Roberge, C.; Yasuda, N. Multikilogram-Scale Synthesis of a Chiral Cyclopropanol and an Investigation of the Safe Use of Lithium Acetylide-Ethylene Diamine Complex. *Org. Process Res. Dev.* **2012**, *16*, 87-95. (o) Stambasky, J.; Malkov, A. V.; Kocovsky, P. Preparation of Boc-protected cinnamyl-type alcohols: A comparison of the Suzuki-Miyaura coupling, cross-metathesis, and Horner-Wadsworth-Emmons approaches and their merit in parallel synthesis. *Collect. Czech. Chem. Commun.* **2008**, *73*, 705-732. (p) Napolitano, C.; Palwai, V. R.; Eriksson, L. A.; Murphy, P. V. Synthesis, kinase activity and molecular modeling of a resorcylic acid lactone incorporating an amide and a trans-enone in the macrocycle. *Tetrahedron* **2012**, *68*, 5533-5540. (q) Scaggs, W. R.; Snaddon, T. N. Enantioselective  $\alpha$ -Allylation of Acyclic Esters Using B(pin)-Substituted Electrophiles: Independent Regulation of Stereocontrol Elements through Cooperative Pd/Lewis Base Catalysis. *Chem. Eur. J.* **2018**, *24*, 14378-14381. (r) Li, P.; Li, J.; Arikian, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. Stereoselective Total Synthesis of Etnangien and Etnangien Methyl Ester. *J. Org. Chem.* **2010**, *75*, 2429-2444. (s) Cui, W.; Mao, M.; He, Z.; Zhu, G. Regioselective and Stereoselective Entry to  $\beta,\beta$ -Disubstituted Vinyl Ethers via the Sequential Hydroboration/Suzuki-Miyaura Coupling of Ynol Ethers. *J. Org. Chem.* **2013**, *78*, 9815-9821. (t) Carreras, J.; Caballero, A.; Pérez, P. J. Alkenyl Boronates: Synthesis and Applications. *Chem. Asian J.* **2019**, *14*, 329-343. (u) Trost, B. M.; Cregg, J. J.; Quach, N. Isomerization of *N*-Allyl Amides To Form Geometrically Defined Di-, Tri-, and Tetrasubstituted Enamides. *J. Am. Chem. Soc.* **2017**, *139*, 5133-5139. (v) Endo, K.; Hirokami, M.; Shibata, T. Stereoselective Synthesis of Tetrasubstituted Alkenylboronates via 1,1-Organodiboronates. *J. Org. Chem.* **2010**, *75*, 3469-3472.
- (14) Examples of failed Arase-Hoshi  $\text{R}_2\text{BH}$ -catalyzed alkyne hydroboration: (a) Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. Studies on the Synthesis of Apoptolidin A. 1. Synthesis of the C(1)-C(11) Fragment. *J. Org. Chem.* **2008**, *73*, 1031-1035. (b) Molander, G. A.; Dehmelt, F. Formal Total Synthesis of Oximidine II via a Suzuki-Type Cross-Coupling Macrocyclization Employing Potassium Organotrifluoroborates. *J. Am. Chem. Soc.* **2004**, *126*, 10313-10318. (c) Ripin, D. H. B.; Bourassa, D. E.; Brandt, T.; Castaldi, M. J.; Frost, H. N.; Hawkins, J.; Johnson, P. J.; Massett, S. S.; Neumann, K.; Phillips, J.; Raggion, J. W.;

- Rose, P. R.; Rutherford, J. L.; Sitter, B.; Stewart, A. M.; Vetelino, M. G.; Wei, L. Evaluation of Kilogram-Scale Sonagashira, Suzuki, and Heck Coupling Routes to Oncology Candidate CP-724,714. *Org. Process Res. Dev.* **2005**, *9*, 440-450.
- (15) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U. Hydroboration: LVIII. Monohydroboration of alkynes with representative dialkylboranes of varying steric requirements. A general synthesis of dialkylvinylboranes. *J. Organomet. Chem.* **1982**, *225*, 63-69.
- (16) (a) Brown, H. C.; Gupta, S. K. Facile redistribution of trialkylboranes with trimethylene borate. A simple, general synthesis of alkaneboronic esters and acids from olefins via hydroboration. *J. Am. Chem. Soc.* **1970**, *92*, 6983-6984. (b) Kanth, J. V. B.; Periasamy, M.; Brown, H. C. New Economical, Convenient Procedures for the Synthesis of Catecholborane. *Org. Process Res. Dev.* **2000**, *4*, 550-553. (c) Hofmeister, H. K.; Van Wazer, J. R. Equilibria in scrambling reactions of some boron compounds. *J. Inorg. Nucl. Chem.* **1964**, *26*, 1209-1213. (d) Köster, R. Transformations of Organoboranes at Elevated Temperatures. *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 174-185, and references therein.
- (17) See: Welianje, N. M.; McGuinness, D. S.; Patel, J. Thermal Dehydroboration: Experimental and Theoretical Studies of Olefin Elimination from Trialkylboranes and Its Relationship to Alkylborane Isomerization and Transalkylation. *Organometallics* **2014**, *33*, 4251-4259, and references therein.
- (18) For catalysis by mechanism II to be effective, intermediate **4** must be significantly more reactive than **2** towards direct hydroboration by **1**.
- (19) (b) Jiang, C.; Blacque, O.; Berke, H. Activation of Terminal Alkynes by Frustrated Lewis Pairs. *Organometallics* **2010**, *29*, 125-133.
- (20) (a) Prokofjevs, A.; Boussonnière, A.; Li, L.; Bonin, H.; Lacôte, E.; Curran, D. P.; Vedejs, E. Borenum Ion Catalyzed Hydroboration of Alkenes with *N*-Heterocyclic Carbene-Boranes. *J. Am. Chem. Soc.* **2012**, *134*, 12281-12288. (b) P. Eisenberger, P.; Crudden, C. M. Borocation catalysis. *Dalton Trans.*, **2017**, *46*, 4874-4887.
- (21) (a) McGough, J. S.; Butler, S. M.; Cade, I. A.; Ingleson, M. J. Highly selective catalytic trans-hydroboration of alkynes mediated by borenium cations and B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>. *Chem. Sci.* **2016**, *7*, 3384-3389.
- (22) The products from Arase-Hoshi hydroboration, as far as we aware, always correspond to a net *cis* addition of H and B.
- (23) see for example: Born, S.; Bacani, G.; Olson, E. E.; Kobayashi, Y. Microwave-Assisted Intramolecular Diels-Alder Reaction towards the Total Synthesis of Symbioimine. *Synlett* **2008**, 2877-2881.
- (24) see for example: Cui, W.; Mao, M.; He, Z.; Zhu, G. Regioselective and Stereoselective Entry to  $\beta,\beta$ -Disubstituted Vinyl Ethers via the Sequential Hydroboration/Suzuki-Miyaura Coupling of Ynol Ethers. *J. Org. Chem.* **2013**, *78*, 9815-9821.
- (25) In the majority of cases, alkynes do not react directly with pure **1**<sub>pin</sub>, even on prolonged heating, see for example references 11j,m,o, and: Lee, C.-I.; Zhou, J.; Ozerov, O. V. Catalytic Dehydrogenative Borylation of Terminal Alkynes by a SiNN Pincer Complex of Iridium. *J. Am. Chem. Soc.* **2013**, *135*, 3560-3566.
- (26) (a) Westcott, S. A.; Blom, H. P.; Marder, T. B.; Baker, R. T.; Calabrese, J. C. Nucleophile promoted degradation of catecholborane: consequences for transition metal-catalyzed hydroborations. *Inorg. Chem.* **1993**, *32*, 2175-2182. (b) Männig, D.; Nöth, H. Contributions to the Chemistry of Boron. Part 160. A Convenient Synthesis of Catecholborane and Diborane. *J. Chem., Soc., Dalton Trans.* **1985**, 1689-1692.
- (27) Chloride sources, such as CH<sub>2</sub>Cl<sub>2</sub>, HCl, Bu<sub>4</sub>NCl, which possibly quench borenium intermediates in the disproportionation mechanisms elucidated by Marder (see reference 26a), also proved effective. Indeed, as little as 15 ppm CHCl<sub>3</sub> induces a noticeable increase in the lifetime of dioxane solutions of (MeO)<sub>2</sub>BH (Burg, A. B.; Schlesinger, H. I. Hydrides of Boron. III. Dimethoxyborane. *J. Am. Chem. Soc.* **1933**, *55*, 4020-4025).
- (28) (a) Brown, H. C.; Zweifel, G. Hydroboration. XI. The Hydroboration of Acetylenes—A Convenient Conversion of Internal Acetylenes into *cis*-Olefins and of Terminal Acetylenes into Aldehydes. *J. Am. Chem. Soc.* **1961**, *83*, 3834-3840. See also reference 15, and: (b) Soderquist, J. A.; Colberg, J. C.; Del Valle, L. The hydroboration of silylacetylenes. The "silyl-Markovnikov" hydroboration route to pure (*Z*)-1-(2-borylvinyl)silanes and beta-keto silanes. *J. Am. Chem. Soc.* **1989**, *111*, 4873-4878. (c) Molander, G. A.; Sandrock, D. L. Utilization of Potassium Vinyltrifluoroborate in the Development of a 1,2-Dianion Equivalent. *Org. Lett.* **2009**, *11*, 2369-2372. Molander, G. A.; Rivero, M. R. Suzuki Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates. *Org. Lett.* **2002**, *4*, 107-109.
- (29) In situ protonolysis of *iso*-**4** / *E*-**4**<sub>pin</sub> with pinacol caused turnover to cease, and generated *p*-F-styrene and *E*-**3**<sub>pin</sub> (1 / 1 ratio) in direct proportion to the initial Cy<sub>2</sub>BH catalyst loading. For analogous protonolysis reactions with pinacol see: Martinez-Fresneda, P.; Vaultier, M. Vinylboronates  $\beta$ -substituted by an electron withdrawing group: synthesis and Diels-Alder reactivity of a new type of electron deficient olefins. *Tetrahedron Lett.* **1989**, *30*, 2929-2932.
- (30) Kanth, J. V. B.; Brown, H. C. Unusual rapid hydroboration of alkenes using diborane in chlorohydrocarbon solvents. *Tetrahedron Lett.* **2000**, *41*, 9361-9364.
- (31) The isotope entrainment analysis is related to catalyst isotope partitioning and pulse-chase analysis, see: (a) Dintzis, H. M. Assembly of the Peptide Chains of Hemoglobin. *Proc. Nat. Sci. Acad.* **1961**, *47*, 247-261. (b) Brown, J. M.; MacIntyre, J. E. Allylic alkylation catalysed by platinum complexes structure and reactivity of intermediates and the overall stereoselectivity. *J. Chem. Soc. Perkin Trans. 2* **1985** 961-970. (c) West, T. H.; Walden, D. M.; Taylor, J. E.; Brueckner, A. C.; Johnston, R. C.; Cheong, P. H.-Y.; Lloyd-Jones, G. C.; Smith, A. D. Catalytic Enantioselective [2,3]-Rearrangements of Allylic Ammonium Ylides: A Mechanistic and Computational Study. *J. Am. Chem. Soc.* **2017**, *139*, 4366-4375.
- (32) This terminology is somewhat analogous to that used in enzymology; see for example: Holbrook, J. J.; Gutfreund, H.; Südi. Kinetic Analysis of Experiments Involving the Single Turnover of an Enzyme. *Biochem. J.* **1976**, *157*, 287-288.
- (33) (a) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. C. Base-Catalyzed Aryl-B(OH)<sub>2</sub> Protodeboration Revisited: From Concerted Proton Transfer to Liberation of a Transient Aryl Anion. *J. Am. Chem. Soc.* **2017**, *139*, 13156-13165; (b) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215-241. (c) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157-167; (d) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* **1980**, *72*, 650-654 (e) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. V. R. Efficient Diffuse Function-Augmented Basis Sets for Anion Calculations. III. The 3-21+G Basis Set for First-Row Elements, Li-F. *Journal of Computational Chemistry* **1983**, *4*, 294-301.
- (34) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Menonucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov,

V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009.

(35) Ignacio Funes-Ardoiz; Robert S. Paton. GoodVibes: Version 2.0.3; Zenodo, 2018. <https://doi.org/10.5281/zenodo.1435820>.

(36) (a) Hübner, A.; Diefenbach, M.; Bolte, M.; Lerner, H.-W.; Holthausen, M. C.; Wagner, M. Confirmation of an Early Postulate: B–C–B Two-Electron–Three-Center Bonding in Organo(hydro)boranes. *Angew. Chem. Int. Ed.* **2012**, *51*, 12514–12518. (b) Kohrt, S.; Dachwitz, S.; Daniliuc, C. G.; Kehr, G.; Erker, G. Stabilized borata-alkene formation: structural features, reactions and the role of the counter cation. *Dalton Trans.*, **2015**, *44*, 21032–21040. (c) Uhl, W.; Er, E.; Hepp, A.; Kösters, J.; Layh, M.; Rohling, M.; Vinogradov, A.; Würthwein, E.-U.; Ghavtadze, N. Treatment of Terminal Alkynes R–C≡C–H with Dialkylaluminum Hydrides: Hydroalumination versus Deprotonation. *Eur. J. Inorg. Chem.* **2009**, 3307–3316.

(37) The analogous hydroboration process shown at the top of Scheme 1 liberates 36.8 kcal mol<sup>−1</sup>, according to in situ reaction calorimetry, see ref 13n.

(38) (Cy<sub>2</sub>BH)<sub>n</sub> is only sparingly soluble in ether solvents: Zweifel, G.; Ayyangar, N. R.; Brown, H. C. Hydroboration. XVII. An Examination of Several Representative Dialkylboranes as Selective Hydroborating Agents. *J. Am. Chem. Soc.*, **1963**, *85*, 2072–2075.

(39) Rau, H. H.; Werner, N. S. Stereocontrolled synthesis of (*E*)-stilbene derivatives by palladium-catalyzed Suzuki-Miyaura cross-coupling reaction. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2693–2696.

(40) Brown, H. C.; Wang, K. K.; Scouten, C. G. Hydroboration kinetics: Unusual kinetics for the reaction of 9-borabicyclo[3.3.1]nonane with representative alkenes. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 698.

(41) (a) Fontaine, F.-G.; Rochette, É. Ambiphilic Molecules: From Organometallic Curiosity to Metal-Free Catalysts. *Accounts of Chemical Research* **2018**, *51*, 454–464. (b) Rochette, É.; Desrosiers, V.; Soltani, Y.; Fontaine, F.-G. Isodesmic C–H Borylation: Perspectives and Proof of Concept of Transfer Borylation Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 12305–12311. (c) Légaré, M.-A.; Courtemanche, M.-A.; Rochette, É.; Fontaine, F.-G. Metal-free catalytic C–H bond activation and borylation of heteroarenes. *Science* **2015**, *349*, 513.

## GRAPHICAL ABSTRACT

